

## EXPERT REVIEW



# The gut microbiome and mental health: advances in research and emerging priorities

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The gut microbiome exerts a considerable influence on human neurophysiology and mental health. Interactions between intestinal microbiology and host regulatory systems have now been implicated both in the development of psychiatric conditions and in the efficacy of many common therapies. With the growing acceptance of the role played by the gut microbiome in mental health outcomes, the focus of research is now beginning to shift from identifying relationships between intestinal microbiology and pathophysiology, and towards using this newfound insight to improve clinical outcomes. Here, we review recent advances in our understanding of gut microbiome–brain interactions, the mechanistic underpinnings of these relationships, and the ongoing challenge of distinguishing association and causation. We set out an overarching model of the evolution of microbiome–CNS interaction and examine how a growing knowledge of these complex systems can be used to determine disease susceptibility and reduce risk in a targeted manner.

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## INTRODUCTION

Relationships between intestinal microbiology and mental health have long been recognised [1]. However, during the past two decades, advances in DNA sequencing technologies and germ-free rodent models, amongst other analytical tools, have greatly improved our ability to characterise the gut microbiome and explore its interaction with host physiology. The application of these approaches has yielded the insight that fundamentally challenges our understanding of how the central nervous system (CNS) is regulated, and has led to a re-examination of risks for neurological and psychiatric disorders and determinants of treatment response.

Since our previous review of gut microbiome–brain research [1], the field has expanded considerably, with a shift in focus from simply identifying microbiome–host associations to exploiting these relationships for clinical benefit. Here, we examine major advances that have occurred since our first review and discuss changing research priorities.

## PREDICTING TREATMENT RESPONSES

Observational studies continue to link features of the gut microbiome with aspects of pathophysiology. For example, recent studies have reported relationships between intestinal microbiology and neurodegenerative disorders, such as Huntington's disease (HD) [2] and multiple sclerosis [3]; psychiatric conditions, such as schizophrenia [4–7] and major depressive disorder (MDD)

[8–11]; and behavioural conditions, including autism spectrum disorder (ASD) [12] and attention-deficit/hyperactivity disorder [13]. These studies, and many others, have resulted in an increasing acceptance that the gut microbiome represents a considerable influence on brain physiology and mental health outcomes and there is growing interest in how this insight can aid effective clinical care, particularly, whether it can enable responses to therapy to be predicted more accurately.

The benefit experienced in response to many common psychiatric medications varies considerably. One-third of those with MDD, for example, are characterised as having 'refractory depression', experiencing no benefit from antidepressant drugs [8], while a similar proportion of schizophrenic patients respond poorly or not at all to antipsychotic medications [14]. The potential for microbiome analysis to predict treatment response is well-illustrated in relation to the use of selective serotonin reuptake inhibitors (SSRIs). While SSRIs are amongst the most commonly prescribed of all medications and are the first-line treatment for MDD and anxiety disorders, the response is highly variable [15]. A growing body of research suggests host–microbiome interactions may play a considerable role in determining the benefit that an individual patient experiences [16].

SSRI use results in alteration of the intestinal microbiome [17–22], a phenomenon that can be explained, at least in part, by the antimicrobial activity common to all SSRIs (reviewed by McGovern et al. [23]). Rather than simply being a treatment side-effect, these microbiological changes appear to be linked to

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efficacy. Using a murine model of depression, escitalopram-associated changes in intestinal microbiology and serum metabolite levels were shown to differ significantly between responsive and non-responsive animals [24]. Similarly, where effective, escitalopram treatment of drug-naïve first-episode MDD in humans is associated with reduced differences in microbiota composition compared to healthy controls [25].

Such links between gut microbiome characteristics and treatment response are not unique to SSRIs, or to those with MDD. Many of the drugs used to treat psychiatric or neurological conditions, including anti-psychotics, tricyclic antidepressants, and benzodiazepines, have antimicrobial activity [18, 26–29], with associated microbiome changes linked to treatment efficacy in some cases. Microbiome changes following risperidone treatment of first-episode, drug-naïve schizophrenia, for example, are predictive of treatment benefit [30].

An interesting aspect of relationships between gut microbiology and treatment response is their potential to contribute to tachyphylaxis [16]. Occurring in around one quarter of SSRI recipients, tachyphylaxis is a phenomenon whereby a decrease in treatment effect occurs after an initial period of benefit, with reduced odds of subsequent efficacious treatment with the same or other types of drugs (as reviewed in detail by Targum [31]). A slowing of treatment-associated microbiome change, or the selection of specific resistance determinants within the microbiome, could both contribute to tachyphylaxis, suggesting that microbiome-targeted mitigation strategies might be worth considering.

Microbiome-encoded enzymes also influence the absorption, distribution, metabolism, and elimination of therapeutic medications by interacting with them directly [32, 33], and by modulating host enzyme activity, thereby influencing drug bioavailability (reviewed in detail by Seeman [34]).

## ESTABLISHING CAUSALITY IN HOST–MICROBIOME RELATIONSHIPS

Establishing whether specific gut microbiome features contribute causally to neurological and psychological conditions or treatment responses remains challenging. Currently, the most common strategy to investigate these relationships is to transplant gut microbiota from patients or preclinical models into germ-free mice to assess the extent to which donor phenotypes are recapitulated, either spontaneously or in response to specific risk exposures. Despite limitations (see Box 1), this strategy is now used widely to investigate the direct contribution of the gut microbiome to conditions such as anxiety and depression, ASD, and neurodegenerative diseases. Below, we highlight notable recent advances in our understanding of direct microbiome influence in these clinical contexts.

### Causal influence in anxiety, anhedonia, and depression

The direct contribution of the gut microbiome to anxiety, anhedonia, and depression was established more than a decade ago [35–37]. However, new research continues to yield important mechanistic insight. For example, transplantation of faecal microbiota from mice subjected to chronic social defeat stress was shown recently to result in increased plasma IL-6, decrease expression of synaptic proteins in the prefrontal cortex, and to trigger an anhedonia-like phenotype in recipient animals [38]. Notably, ingestion of *Lactobacillus intestinalis* or *Lactobacillus reuteri* was shown to be sufficient to achieve this effect, which could be prevented by subdiaphragmatic vagotomy [38]. Gut microbiota variations achieved through embryo transfer into parents from different animal vendors, a common phenomenon for divergent gut microbiota phenotypes in mouse-based studies, has also been shown to result in divergent behaviour phenotypes including locomotor activity, exploratory behaviour, and anxiety, in recipient animals [39].

### Box 1. The ecological complexity of the human gut microbiome

The gut microbiome is a complex and dynamic ecosystem. Its characteristics are defined by the interplay between extrinsic factors (such as diet and exposure to pharmaceuticals), intrinsic factors (e.g., genetics, pathophysiology, host secretions), and the collective traits of microbial species that colonise an individual. Importantly, the nature of the gut ecosystem is distinct from that of the individual microbial taxa that comprise it. Through a network of microbe–microbe and host–microbe interactions, the gut microbiota is capable of substrate decomposition and metabolite biosynthesis pathways that no individual member can replicate in isolation. Moreover, considerable functional redundancy exists, whereby the same process can be performed by many different microbes, through many different pathways. An example relevant to the gut–brain axis is the microbial production of short-chain fatty acids (SCFAs). Many gut anaerobes produce lactate and acetate through carbohydrate fermentation, while a smaller number can convert acetate into butyrate, or lactate into propionate, through multiple biosynthetic pathways [195]. Net intestinal SCFA concentrations reflect the relative utilisation of these pathways and of others involved in the onward conversion of SCFAs into other products [196]. Predicting the intestinal SCFA levels to which the host is exposed therefore depends on microbiome-wide assessments of microbial functionality.

The complexity of the gut microbiome also allows it to remain highly stable over long periods, resisting perturbations and rapidly reverting to pre-exposure configurations, while at the same time, being capable of shifts in composition to adapt to selective pressures, such as changes in diet. However, while often stable within an individual, considerable differences in gut microbiota exist between individuals, as well as between locations within the gut (e.g., along the length of the gut, and between luminal and epithelial populations). This complexity makes accurately determining functional capacity, predicting response to intervention, or developing targeted strategies for microbiota modification, extremely challenging, a factor that is further compounded in humans by variation in genetics, diet, antimicrobial exposure, and lifestyle in humans (factors that are largely absent in highly conserved animal models).

Inter-individual differences in microbiota composition are exaggerated in disrupted, disease-associated microbiota. As a consequence, the majority of the clinical trials of interventions that aim to provide clinical benefit in relation to mental health through microbiome modification have had underwhelming results. However, our ability to predict how an individual's gut microbiome will respond to different exposures, and to factor such information into clinical trial design and disease risk prediction, is expanding rapidly as a result of increasingly sophisticated *in silico* modelling approaches [197].

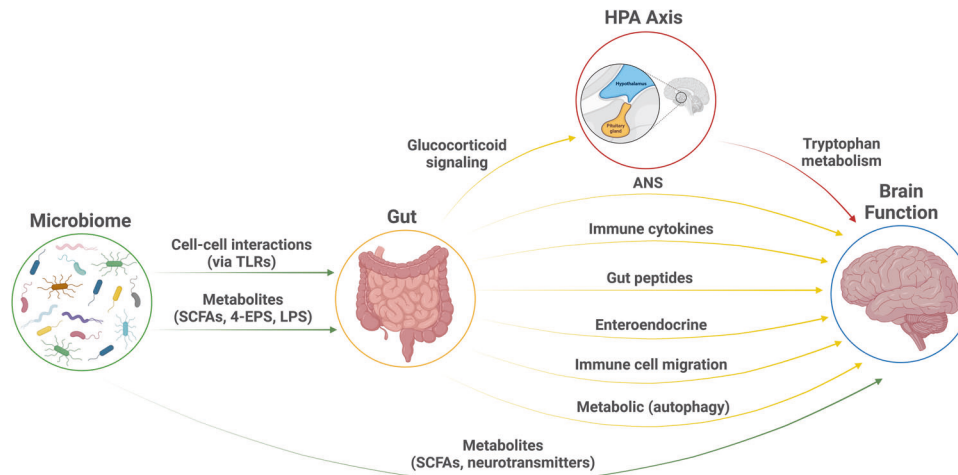
### Causal influence in autism spectrum disorder

The incidence of ASD has increased considerably in recent decades [40], as has the evidence of direct gut microbiome involvement in its development. For example, deletion of the autism-associated Ephrin type-B receptor 6 gene (EphB6) was shown recently to result not only in autism-like behaviour, but also alteration of the gut microbiota in mice [41]. Transplantation of the faecal microbiota from EphB6-deficient mice was sufficient to give rise to autism-like behaviour in antibiotic-treated recipient mice, while the instillation of wild-type microbiota ameliorated autism-like behaviour in EphB6-deficient recipients [41]. Similar effects have been reported following the transplantation of gut microbiota from ASD human donors into germ-free mice, including recapitulation of hallmark autistic behaviours and alternative splicing of ASD-relevant genes in the brain [42].

### Causal influence in neurodegenerative diseases

A growing body of research supports the causal contribution of host–microbiome interactions to neurodegenerative diseases. Transplantation of gut microbiota from Parkinson's disease (PD) mice into germ-free recipients, for example, results in increased motor dysfunction [43], while transplantation into wild-type recipients also results in impaired motor function and decreased striatal dopamine and serotonin levels [44]. Conversely, transfer of gut microbiota from wild-type mice to PD recipients has a neuroprotective effect [44].

Similar findings have been reported in relation to other forms of dementia, including Alzheimer's disease (AD) where instillation of faecal microbiota from wild-type mice ameliorates the formation of amyloid-beta plaques and neurofibrillary tangles, glial reactivity and cognitive impairment, as well as reversing abnormalities in the colonic expression of genes related to intestinal macrophage



**Fig. 1 The microbiome–gut–brain axis: active communication pathways connecting the microbiome and the central nervous system to affect brain function.** 4-EPS 4-ethylphenyl sulfate, ANS autonomic nervous system, HPA hypothalamic-pituitary-adrenal, LPS lipopolysaccharide, SCFAs short-chain fatty acids, TLR Toll-like receptor.

activity and the circulating blood inflammatory monocytes [45]. Moreover, despite its clear genetic basis, clinical features of HD have also been shown to be influenced by specific bacterial taxa associated with cognitive performance and inflammation [2, 46, 47]. Whilst current evaluations on these relationships have been reliant predominantly on gut microbiota transplants, we are unravelling the precise mechanisms involved.

#### OUR GROWING UNDERSTANDING OF THE MECHANISM

The gut microbiome can influence neurophysiology and CNS function through many different pathways (Fig. 1). Our growing understanding of the mechanisms of communication, such as the microbial production of short-chain fatty acids (SCFAs), the vagus nerve stimulation, tryptophan production, and the triggering of cytokine release, continues to grow. In addition, several new potential pathways have recently been proposed.

#### Autonomic nervous system

The vagus nerve is a crucial pathway for bidirectional communication between the gut microbiome and the CNS and was amongst the first such pathways to be identified. Enteroendocrine cells in the gut have been shown to form glutamatergic synapses with vagal villus afferents in the small intestine [48], and the distal colon [49], enabling a single synaptic connection from the gut to the brain. Gut-innervated vagal afferents have also been identified as key components in host reward circuitry, directly triggering dopamine release in the striatum [50]. While vagal afferent fibres are distributed to all layers of the intestinal wall, they do not cross the epithelium, and therefore do not interact directly with the gut microbiota [51, 52]. However, vagal afferent fibres can sense microbiota signals indirectly through the diffusion of bacterial metabolites [53], through microbially-induced production of host factors, such as gut serotonin [48], and via the intestinal epithelial cell production of peptides that can occur in response to bacterial metabolites, such as indole [54, 55]. Stimulation of the vagus nerve is relayed to the brainstem and onwards to other areas of the brain via the nucleus tractus solitarius [56], with consequences for a range of different clinical conditions [38, 56–60]. In particular, depression-like phenotypes arise from *L. reuteri* and lipopolysaccharide (LPS) instillation in a vagus nerve-dependent manner [38, 58]. Conversely, *L. reuteri* and *L. intestinalis* also elicit beneficial neurological effects by rescuing social behavioural deficits in models of ASD with an intact vagus nerve [57, 60]. Perhaps contributing to the conflicting effects of *Lactobacillus* is the

significant impact of the vagotomy procedure, whereby both afferent and efferent fibres of the vagus nerve are severed, and it is the procedure itself that alters brain function [61]. Furthermore, impairing vagal integrity increases the severity of inflammation [61, 62], which may explain the elevated inflammatory effects of *Escherichia coli* and *Paenaltaligenes hominis* in cognitive impairment models that remain following vagotomy [59].

Tryptophan, a diet-derived amino acid, is essential for synthesis of serotonin (5-HT) in the CNS and in the gut, and for the production of neuroprotective and neurotoxic components through the kynurenine pathway [1]. The importance of tryptophan metabolism in the development of psychiatric disorders is well-established and was again highlighted by a recent meta-analysis of more than 100 studies and over 10,000 participants that identified reductions in tryptophan and kynurenine in MDD, bipolar disorder, and schizophrenia [63]. Tryptophan availability is strongly influenced by the gut microbiota and links between changes in microbiome functionality and disease continue to be identified. For example, the recent analysis of gut metagenomes from individuals with bipolar disorder and depression has revealed changes in seven specific functional pathways involved in tryptophan biosynthesis and metabolism [64].

Our understanding of microbiome–brain communication via the hypothalamic-pituitary-adrenal (HPA) axis also continues to grow. During stress, the release of high levels of glucocorticoids impacts the HPA axis and decreases adult hippocampal neurogenesis [65, 66]. This relationship is reflected by the decrease in neuronal differentiation and maturation in the hippocampus associated with the glucocorticoid, dexamethasone [67]. Indeed chronic glucocorticoid exposure may underlie the vulnerability of the hippocampus to chronic stress-induced reductions in neurogenesis via corticosterone [67]. Recently, it was shown that transplantation of gut microbiota from humans with severe depression into germ-free mice resulted in changes in the hippocampal expression of six glucocorticoid receptor pathway genes (*Slc22a5*, *Aqp1*, *Stat5a*, *Ampd3*, *Plekhf1*, and *Cyb561*) [68] that are responsible for intracellular signalling of cytokine cell surface receptors and cellular growth [69], production of neurotransmitters [70], and ATP energy production in the brain [71]. *Enterococcus faecalis* has been shown to promote social activity and reduces corticosterone levels by suppressing activation of the HPA axis following overactive social stress in mice [72], an effect that can be blocked by antibiotic depletion of gut microbiota, and restored by adrenalectomy, antagonism of glucocorticoid receptors, or pharmacological inhibition of corticosterone synthesis [72].

## Immunity and inflammation

Our immune system is critical for the maintenance of healthy neuronal networks and the clearance of cellular debris, and immune dysregulation and chronic inflammation are strongly associated with increased risk of psychiatric and neurodegenerative disorders [1]. The microbiome influences immunity both through the interaction of microbial products with host receptors in the gut to trigger circulation of proinflammatory cells and cytokines and through systemic translocation of microbial products to interact with host cells in the brain directly. Microbiome-derived SCFAs are involved in both of these processes. Amongst their many roles, SCFAs interact with intestinal epithelial cells and immune cells, including neutrophils, to regulate gut barrier function and intestinal mucosal immunity [73, 74], and modulate the production of inflammatory cytokines, chemokines, and lipid mediators [75]. Acetate and propionate activate receptors on neutrophils, and have been shown to influence the production of circulating inflammatory cytokines, including TNF- $\alpha$  [76]. SCFAs can also pass through the intestinal mucosa to enter systemic circulation, before crossing the blood–brain barrier to influence innate immune cells, including microglia and astrocytes, in the brain [77].

Interactions between SCFAs and innate immune cells are commonly mediated by G protein-coupled receptor 41 in the case of acetate, propionate, and butyrate, and also by GPR43 in the case of acetate and propionate [74, 78]. However, these receptors are not necessary for SCFAs to enter the CNS, nor are they expressed by microglia or other CNS immune cells [77]. Instead, propionate, butyrate, and acetate all appear to influence microglia directly through intracellular inhibition of histone deacetylases, resulting in enhanced transcription of specific factors relating to microglial function [43, 77].

SCFAs are not unique in directly regulating CNS immunity, and indeed many other microbial products from the gut can also cross the blood–brain barrier to influence CNS immune regulation. Detection of peptidoglycan by specific pattern-recognition receptors in the developing prefrontal cortex, striatum, and cerebellum, for example, has been shown to influence patterns of synaptogenesis [79]. Another example is LPS, which interacts with Toll-like receptor (TLR)-4 to trigger proinflammatory signalling within microglia via the nuclear factor- $\kappa$ B (NF- $\kappa$ B) pathway, resulting in upregulation of proinflammatory cytokines IL-1 $\beta$ , IL-6, and TNF- $\alpha$ , and activation of CX3CR1, a membrane-bound chemokine receptor on microglia [80–82]. This process has been shown to influence the synaptic pruning that is implicated in the development of neurodegenerative and psychiatric conditions [82–84].

The gut microbiome also plays an important role in the peripheral activation of immunity. Prior to birth, gut commensal bacteria prime CD4<sup>+</sup> T helper (T<sub>H</sub>17) cells in pregnant mice and elicit a proinflammatory response via production of IL-17A, which may increase the likelihood of offspring developing neurodevelopmental disorders [85]. Shortly after birth, microbially-produced LPS induce IL-17A release by T<sub>H</sub>17 cells in the meninges that activate cortical glutamatergic neurons, resulting in anxiety-like behaviour in mice [86]. Reciprocally, the intestinal administration of IL-17A to mouse models of multiple sclerosis has also been shown to directly alter the gut microbiome into a proinflammatory state that disrupts tissue barrier integrity, contributing to systemic inflammation [87]. In a recent study, IgA-secreting plasma cells were shown to be activated in the intestine before migrating to the meninges that surround the brain and spinal cord to play a crucial role in protecting the CNS at the venous barrier [88]. This process, which increases with age and as a result of breaches of the intestinal barrier, is impaired if the gut microbiota is depleted [88].

In addition to regulators of host immunity, other microbiome-derived products can translocate from the gut to influence the

CNS, including peptides and neurotransmitters. The importance of this pathway was highlighted by a recent study that reported that the capacity of the gut microbiome to synthesise dopamine metabolites and gamma-aminobutyric acid (GABA) correlated positively with mental quality of life and depression [89]. Similarly, exposure of diet-induced obese mice to antibiotics results in reduced anxiety and depression traits, altered levels of tryptophan, GABA, brain-derived neurotrophic factor, and decreased insulin signalling and inflammation in the nucleus accumbens and amygdala of the brain [90], an effect that further implicates the gut microbiome in the increased rates of anxiety and depression commonly associated with obesity and diabetes in humans [91].

## Endocrine system and enteroendocrine cells

The intestinal epithelium senses nutritional and microbial stimuli via epithelial enteroendocrine cells (EECs), which project long, pseudopod-like processes to directly interact with intestinal neurons and epithelial cells [92, 93]. A subset of EECs also directly synapse with vagal neurons and activate afferent synaptic transmission for rapid communication with the brain [49, 94]. EECs collectively comprise the largest endocrine system of the body [95, 96], and contain a number of subtypes based on their production of a myriad of different hormones and neurotransmitters. These include, but are not limited to, glucagon-like peptide 1 (GLP-1), peptide YY (PYY), cholecystokinin (CCK), substance P, and 5-HT. The use of germ-free and antibiotic-treated mouse models, as well as faecal microbiome transplants, have highlighted a causal role of gut microbiota to changes in gut-derived hormone levels, particularly in the context of mental health [97].

The most abundant EEC subtype are enterochromaffin (EC) cells, which exist along the length of the gut and produce ~95% of the body's 5-HT [98]. The presence of a gut microbiome doubles EC cell density and circulating 5-HT levels in a chronic setting [99–101], while acute exposure to microbial metabolites, such as indole, isobutyrate and isovalerate, activate EC cells and trigger 5-HT secretion, which in turn stimulate vagal sensory ganglia and activate cholinergic enteric neurons [55, 94]. EC cells directly sense gut microbiota and their metabolites, via the expression of a suite of receptors including FFAR2, FFAR3, TRPA1, Olfr558, and TLR2 [94, 102–105]. Of note, the relative expression of these receptors and their functional responses is dependent on where EC cells are located along the gut [105], highlighting region-dependent mechanisms for microbe-EC cell interactions and downstream gut–brain signalling pathways.

In addition to its role in regulating feeding behaviour [106], therapeutic targeting of GLP-1 signalling via GLP-1 receptors is now being considered in the context of mood disorders and neurodegenerative diseases (reviewed by Detka and Glombik [107]). Recently, GLP-1 secretion and action has been identified to be mediated by the presence of intestinal microbiota and microbial metabolites, with subsequent activation of afferent nerve fibres in the colon [54, 108]. Knowledge regarding how pulsatile release of microbial metabolites, which follow circadian rhythms largely centred around feeding [109–111], can drive endogenous rapid gut–brain signalling to impact host behaviour or brain function is currently lacking.

CCK- and PYY-expressing cells also contain pre-synaptic markers and synapse directly with neurons to communicate centrally via the vagus nerve [49]. The direct communication between EECs and neurons is thought to be a route for the pathogenic migration of  $\alpha$ -synuclein from gut to brain in PD, with  $\alpha$ -synuclein expression being enriched in CCK- and PYY-expressing EECs that are synaptically connected to neurons shown to also contain  $\alpha$ -synuclein [112]. This is supportive of the Braak hypothesis that PD arises within the gut and spreads to the brain via the vagus nerve [113].

A bidirectional relationship exists between gut microbiota and gut-derived hormones. Alterations to 5-HT production are now



recognised to drive microbial diversity and composition [22, 114–116], particularly members of the bacterial phylum, Firmicutes. *Turcibacter sanguinis* expresses a eukaryotic neurotransmitter sodium symporter-related protein that shares sequence and structure with the mammalian 5-HT transporter [22]. The use of SSRIs can therefore both directly and indirectly impact microbial composition—indirectly via increases in 5-HT availability to bacteria and directly via inhibition of bacterial SERT-like transporters.

### Novel pathways

New mechanisms of communication between the gut microbiome and the CNS continue to be identified. There is growing interest, for example, in the role of autophagy in maintaining mental health, particularly in relation to neurodegenerative disorders. Autophagy is a ubiquitous intracellular process that acts to regenerate nutrients from macromolecules in response to nutrient deprivation and clears unwanted or damaged material from the cell through lysosomal degradation [117]. Notably, in addition to nutrient starvation, infection, and hypoxia [118], the gut microbiome also appears to be an important regulator of autophagy. SCFA biosynthesis increases this process by promoting histone hyperacetylation [119, 120], while LPS from the cell walls of Gram-negative bacteria stimulates autophagy in macrophages through interaction with TLRs [121, 122]. In AD, neuronal autophagy is involved in the degradation of neurofibrillary tangles composed of hyperphosphorylated and misfolded tau protein within the brain [123]. In a mouse model, deficiency in autophagosome biosynthesis has been shown to polarise murine microglia to a proinflammatory state and enhance intraneuronal tau pathology [124]. In addition to AD, altered regulation of autophagy has been implicated in PD, HD, and amyotrophic lateral sclerosis [125, 126].

The endocannabinoid system is another pathway that is increasingly recognised as an important mediator of microbiome–brain interactions. Involved in numerous aspects of physiology [127, 128], the roles of the endocannabinoid system include modulation of CNS responses to stressors via a signalling system comprising of cannabinoid receptors, the mediator molecules N-arachidonylethanolamine and 2-arachidonoylglycerol, and the enzymes involved in the synthesis and degradation of these ligands [128]. Colonisation studies in germ-free mouse models have implicated small intestine microbiology in the regulation of endocannabinoid system genes, including *Cnr1* and *Gpr55*, which are associated with gastrointestinal dysfunction and chronic stress [128]. A cohort study investigating anhedonia and amotivation identified those with more severe anhedonia/amotivation to have increased levels of palmitoylethanolamide (PEA), the endogenous equivalent of cannabidiol, as well as reduced microbial diversity [129]. PEA acts as an inhibitor of the fatty acid amide hydrolase, which is the main catabolic enzyme of endocannabinoid agonists. Endocannabinoid agonists are protective towards mental health by regulating feedback at the synaptic level to maintain excitatory and inhibitory balance in the brain [130]. Furthermore, the intertwined endocannabinoid system connects with the liver, pancreas, muscles, and adipose tissue, affecting peripheral immunity and metabolism [127], potentially acting as pathways of indirect microbial influence on the CNS.

### Pathway overlap and crosstalk

There is considerable overlap and crosstalk between microbiome–brain communication pathways. For example, neuro-pathological and immunopathological mechanisms affecting the CNS have been shown to be mediated by type-I interferon signalling [131] and dietary metabolites, including tryptophan [132]. The type-I interferon IFN- $\beta$ , or dietary tryptophan, induces the expression of the aryl hydrocarbon receptor (AHR) in astrocytes, which mediates the reduction of CNS inflammation [132]. Bacterial enzymes, particularly those derived from

commensal gut microbes, have been shown to convert tryptophan into metabolites that act as AHR agonists [133], including indoxyl-3-sulfate [134], indole-3-propionic acid and indole-3-aldehyde [133], thereby modulating astrocyte functioning on the CNS [132].

Similar interactions have been observed in rats showing depression-like behaviours following chronic stress [105]. Upon receiving faecal microbiota transplant from control rats, depression-like behaviours are ameliorated, with increases in serotonin, and decreases in proinflammatory cytokines IL-1 $\beta$  and TNF- $\alpha$  that are normally indicative of microglial and astrocytic activation [135]. The reduction in activated microglia and astrocytes corresponds to reduced expression of NOD-like receptor protein 3 (NLRP3), ASC, and Caspase-1 in the prefrontal cortex and hippocampus [135]. Responsible for modulating proinflammatory cytokine levels, NLRP3 is increasingly being linked to activation in the brain and communication by gut microbes, with the abundances of Firmicutes, Proteobacteria and Bacteroidetes implicated to NLRP3-regulation of glial dysfunction [136, 137].

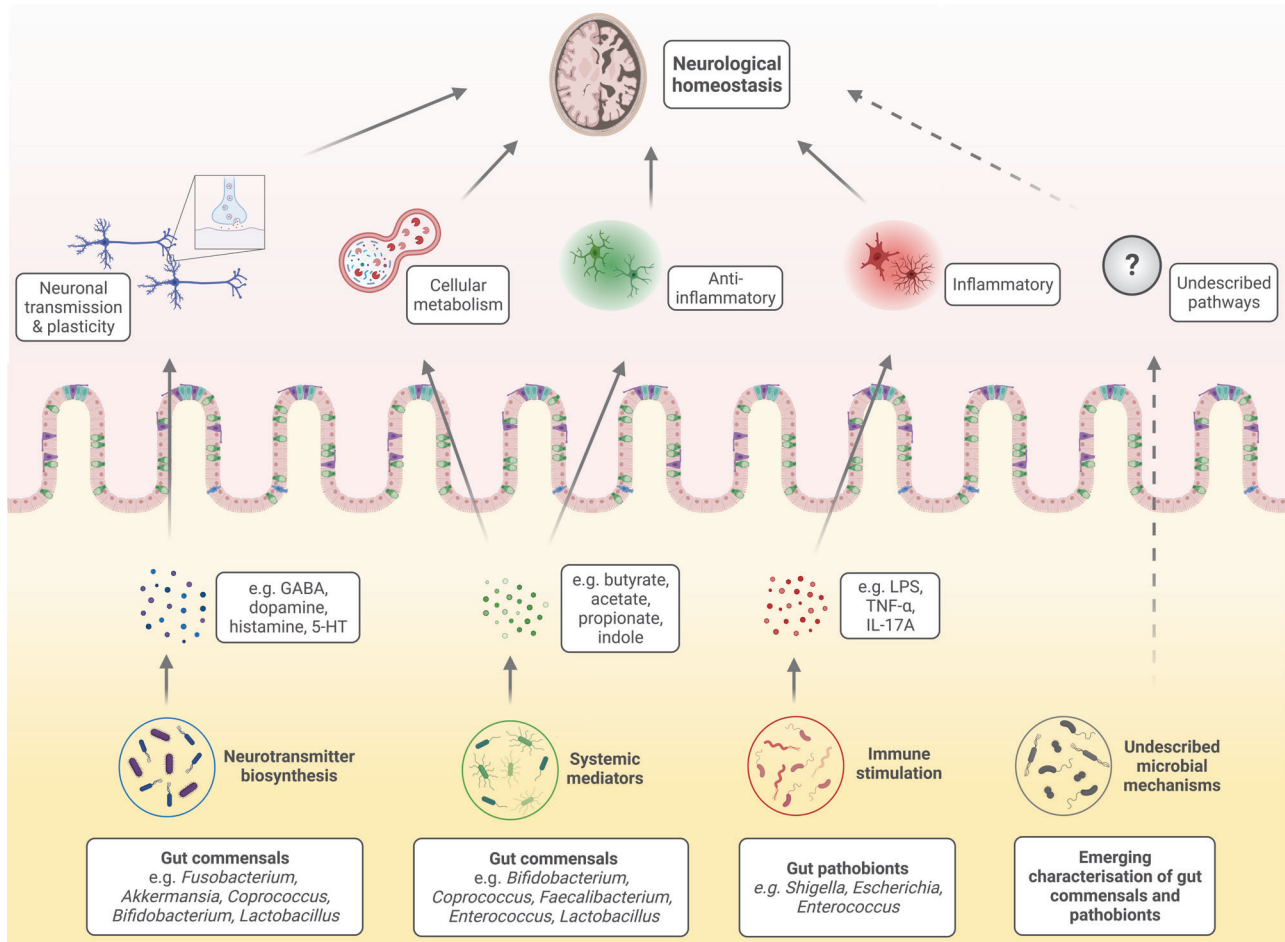
Interconnection of these systems has been investigated further by the administrations of *L. rhamnosus* to mice that have undergone subdiaphragmatic vagotomy. *L. rhamnosus* administration to sham surgery mice resulted in reduced anxiety-like behaviour (compared to vagotomised mice), which appeared to also have an effect via the HPA axis, with reduced plasma corticosterone measured following acute stress, and decreases in activated microglia in the hippocampus [62]. Vagotomy alone led to a significant increase in activated microglia in the hippocampus that was not altered with *L. rhamnosus* treatment, indicating both microbe-induced and vagal signalling influence endocrine and immune components of the microbiota–gut–brain axis.

In summary, the known key functional pathways resultant of these microbiome–host regulatory pathways that mediate neurological health and disease are illustrated in Fig. 2. For recent and detailed descriptions of relationships between specific taxa and regulatory pathway components, see [138–140].

## THE INFLUENCE OF EXPOSURES AND THE REDUCTION OF DISEASE RISK

Microbiome characteristics help to shape CNS function [1, 141, 142]. Shifts in intestinal microbiology result from both external exposures, including diet, enteric infection, and exposure to therapeutic drugs, and intrinsic factors, such as enteric pathology or ageing. Understanding how these exposures influence intestinal microbiology can help to identify those at greatest risk of disease, and guide the development of effective risk reduction strategies.

Relationships between diet and mental health risks have long been recognised [143]. Diet shapes microbiome characteristics and informs associated chronic disease risk [144, 145], including neurological or psychiatric conditions [146–149]. Broadly, consumption of what is often termed a ‘Western’ diet (rich in refined sugars and saturated fats) is associated with altered microbiota composition, reduced gut barrier function, altered neurotransmitter metabolism, and increased mental health risks [150–153]. However, specific dietary components have also been shown to exert an influence on susceptibility to neurological or psychiatric conditions. For example, a recent study of food product consumption in more than 1100 individuals with and without psychiatric disorders identified nitrated cured meats to be associated with a markedly increased rate of hospitalisation for acute mania [154]. A follow-up investigation in rats showed that feeding commercially available nitrated meat or a purified fixed-nitrate diet resulted in mania-like changes to locomotor and novelty-associated hyperactivity [154].



**Fig. 2 The known key functional pathways of gut microbes that mediate neurological homeostasis.** Perhaps more significant than the sole identification of individual microbes linked to neurological disease is the emerging appreciation of their collective functional impact on neuropathophysiology. Members of the *Bifidobacterium* genus, for example, synthesise the short-chain fatty acid metabolite, butyrate, that influences both neuronal plasticity and systemic immunity. Clostridia and lactobacilli both produce multifunctional metabolites, such as butyrate, and metabolise amino acids to produce neurotransmitters, while pathobionts within the gut microbiota, such as *Escherichia coli*, can promote the development of systemic inflammatory states. However, as yet, we understand only a fraction of the potential microbiome–host regulatory pathways that influence the central nervous system, with new insight continuing to emerge through ongoing studies. 5-HT serotonin, GABA gamma-aminobutyric acid, IL-17A interleukin 17A, LPS lipopolysaccharide, TNF- $\alpha$  tumour necrosis factor- $\alpha$ .

Not surprisingly, foods that promote SCFA biosynthesis through carbohydrate fermentation in the colon continue to be associated with reduced neuroinflammation in animal models [155, 156], a relationship that is supported by both observational and interventional studies in humans [157, 158]. Reciprocally, poor habitual diet appears to be associated with poor mental health outcomes. A prospective study involving more than 14,000 Spanish university graduates, for example, reported a significant association between the consumption of ultra-processed foods and depression [159]. There is also a growing appreciation that maternal dietary exposures are important in shaping foetal and early postnatal development, including immune maturation and brain development [160–162].

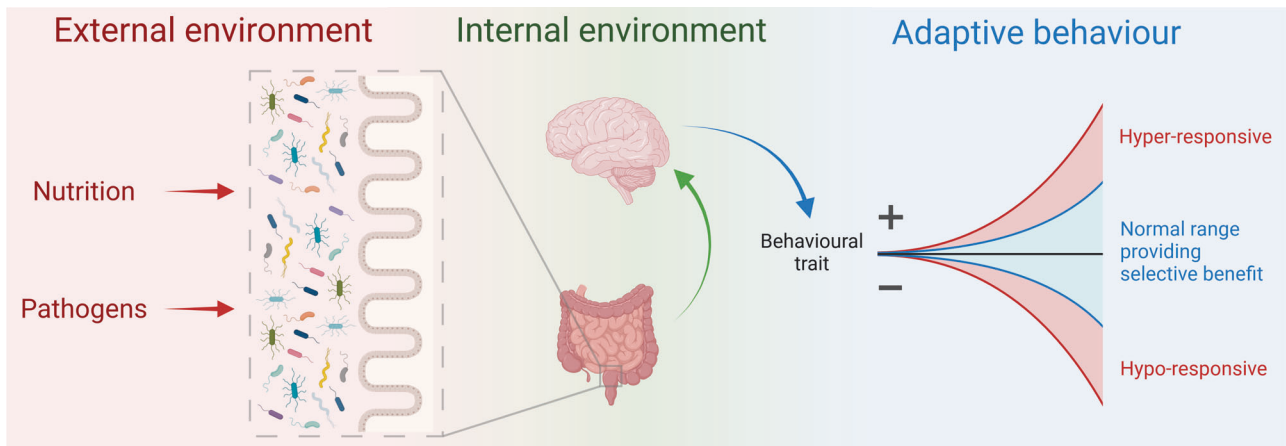
A wide range of other non-dietary exposures can also influence intestinal microbiology, and as a consequence, mental health risks. For example, the immune-mediated impairment of social and emotional cognition associated with alcohol use disorder appears to occur, at least in part, through microbiome-mediated pathways [163–166]. Pharmaceutical exposures are also likely to exert a considerable indirect influence. For example, metformin, the first-line medication for type 2 diabetes, has been shown in a high-fat diet consumption-induced obesity mouse model to restore the impairment of neurogenesis in the dentate gyrus and to prevent the cognitive decline of the obese mice, potentially through inhibition of

microglia activation and neuroinflammation in the brain [167]. The potential to influence the CNS in this way has now been described for a wide range of pharmaceutical drug classes [28].

Intrinsic risk factors may also act via microbiome-mediated mechanisms. Alterations in intestinal microbiology have been shown to be sufficient to induce both peripheral and central inflammatory processes and cognitive deficits associated with sleep deprivation (SD), acting via the TLR-4/NF- $\kappa$ B signalling pathway to impair cognitive function [168]. The gut microbiome also contributes to the relationship between age and the risk of neurodegenerative diseases through the development of chronic inflammation, or ‘inflammaging’ [169–171]. While intrinsic risk factors are not readily modified, the involvement of the gut offers an important opportunity for targeted risk reduction for the estimated 40% of worldwide dementia incidence that arises through modifiable risk factors [172].

#### THE GUT MICROBIOME–BRAIN AXIS: A SELECTIVE ADVANTAGE IN A CHANGING ENVIRONMENT

While it is now widely accepted that the gut microbiome–brain axis acts as an important regulator of the human CNS, and its response to external stimuli, there has been relatively little discussion to date of why such a phenomenon exists at all. The



**Fig. 3 The evolutionary basis of microbiome–host interactions.** The gut microbiome–brain axis enables shifts in host physiology or patterns of behaviour in response to changing external circumstances. In particular, it is the action of our microbiome to nutritional availability and pathogen exposure that drives our behavioural response. It is the presence or absence of these modifiable risk exposures that, when combined with genetic predisposition and other risk factors, drive responses out of the ‘normal’ range and into potentially pathological behaviour.

proliferation of pathways by which a critical component of human physiology is sensitive to slight changes in microbial cues would seem to present considerable risks. To persist, these risks associated with such pathways must be exceeded by the selective advantages that they confer on the host. Here, we outline a proposed framework that could explain the existence and evolutionary basis of the gut microbiome–brain axis.

The gut microbiome–brain axis enables shifts in host physiology or patterns of behaviour in response to changing external circumstances (Fig. 3). In evolutionary terms, the two principal determinants of human survival are the availability of nutrition and exposure to pathogens, both factors that are associated with behavioural responses. For example, infectious disease in mammals commonly results in significant reductions in social interaction, in turn, minimising opportunities for transmission [173], while nutritional limitation is associated with increased aggression, impulsivity and risk-taking, mediated by a range of macronutrient-specific mechanisms [174]. Notably, nutritional groups that have been shown to be potent modulators of aggressive behaviour, such as cholesterol, tryptophan, phytoestrogens, and fermentable carbohydrates [174–176], are all macronutrients that are known to undergo substantial modification within the colon to produce neuro- and immune-modulatory compounds [1, 174].

Why then might a selective advantage such as the ability to respond to external stimuli be implicated so widely in psychopathology? Development of neuropathy or mental illness via microbiome–brain communication pathways likely occurs in individuals where modifiable risk exposures combine with a genetic predisposition. At a population level, significant changes in risk exposures, including increased consumption of refined sugars and saturated fats, greater life-expectancy, and a reduced burden of infectious disease, are likely to be reflected in the epidemiology of neurodegenerative and psychiatric conditions [177–179]. Moreover, microbiome-mediated changes can interact with intrinsic risks, such as genetic risk factors and ageing. For example, 70% of genetic features of ageing fail to occur in drosophila raised gnotobiotically [180], while disruption of gut microbiota in mice during early life through exposure to antibiotics results in impaired immunity, increased insulin resistance, evidence of increased inflammaging in later life, and reduced lifespan [181].

We conceptualise the gut microbiome–brain axis as a set of mechanisms that confer a significant selective advantage by enabling the CNS to adapt physiology and higher behaviour to our circumstances. This model not only allows us to eavesdrop on

microbiome–host communication in order to predict disease risk, but also presents novel opportunities to influence the regulation of the CNS directly.

#### MICROBIOME-TARGETED INTERVENTIONS TO IMPROVE MENTAL HEALTH OUTCOMES

Unlike genetic predisposition, social determinants, or ageing, interactions between the intestinal microbiome have the potential to be modified relatively easily. There are a number of potential strategies in this regard: (1) modification of gut microbiota, (2) altering microbiome metabolic output, (3) targeting host responses to microbiome-derived factors, or (4) blocking or enhancing microbiome-mediated host mechanisms. To date, research has largely focused on the first two of these options, either through the introduction of potentially beneficial microbes in the form of probiotics or through the use of dietary or prebiotic strategies.

Probiotic research in relation to mental health has been the subject of a number of recently detailed narrative and systematic reviews [182, 183], including specific conditions, such as schizophrenia [184] and MDD [185]. As yet, evidence supporting specific probiotics, and to an even greater extent, prebiotics, remains limited [186–189]. While dietary interventions more generally have also been considered as a means to promote normal neural development and CNS function [146, 190], assessing the effects of dietary exposures at a population level is challenging. The ecological complexity of the response of the gut microbiome to a specific dietary measure (Box 1), as well as the links between diet and other mental health risk factors, particularly social determinants [191, 192], require careful consideration. Large interventional studies have however provided clear evidence of the potential of dietary measures. For example, a study of a 12-month Mediterranean diet (NU-AGE diet) in more than 600 non-frail or pre-frail elderly subjects across five European countries reported microbiome enrichment with bacterial taxa that are positively associated with markers of lower frailty and improved cognitive function, and negatively associated with inflammatory markers including C-reactive protein and IL-17 [158].

#### Faecal microbiota transplantation (FMT)

Much of the evidence of causal associations between altered intestinal microbiology and CNS regulation is based on studies in which gut microbiota from the animal model or human donors has been instilled into germ-free or antibiotic exposed mice. The

**Box 2.** Limitations of microbiota transplantation into germ-free mice to demonstrate causality

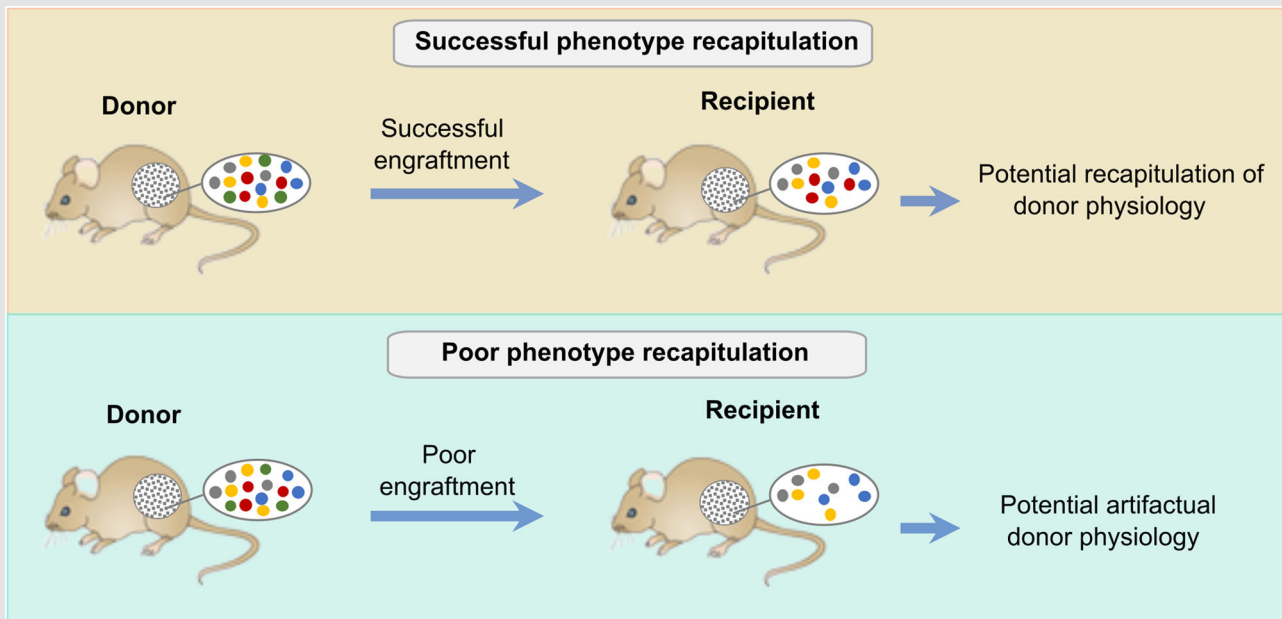
Microbiota transplantation experiments have been used widely to provide evidence of causality in associations between microbiome features and neurological or psychiatric conditions (reviewed in detail by Yang et al. [8]). These include demonstrations that instillation of material from patients or disease models is sufficient to recapitulate pathophysiology, and that instillation of material from healthy donors can ameliorate it. However, despite our reliance on these approaches, they have limitations that should be considered.

Both germ-free and antibiotic-treated mice are commonly used, and each has advantages and weaknesses. Germ-free mice are costly to maintain and require specialist facilities. In addition, the absence of microbiota has during critical developmental stages in early life resulted in substantially altered physiology. In contrast, antibiotic ablation is a cheap and relatively simple strategy, where incomplete it can result in overgrowth by opportunists, such as *Enterobacter* species.

However, common to both approaches is the need for strict anaerobic processes of donor material to protect the strict anaerobes that make up the majority of the commensal gut microbiota. Failure to do this can skew composition towards facultative anaerobes that are common features of disease-associated microbiota.

Other considerations are the number of repeat microbiota instillations required to successfully reproduce the donor microbiota, the time required for microbial succession before assessments of physiology can be made, the influence of coprophagia in co-housed mice, and the extent to which human microbiota can be replicated in a mouse, whose intestinal physiology and diet are considerably different. Replication of donor microbiota in recipients is inevitably imperfect [198, 199]. However, assessment of composition prior to experimentation is essential. Moreover, the impact of partial success, and altered microbiome functionality, must be considered relative to the disease context being investigated.

Perhaps most importantly, while microbiota transplantation can be helpful in demonstrating where features of intestinal microbiology are sufficient to precipitate host responses, it is less able, in the absence of realistic models, to show where microbiology is insufficient on its own, but nonetheless exerts a powerful influence through its interactions with other exposures or host risk factors.



potential therapeutic benefit of transplanting healthy faecal microbiota has also been demonstrated in mice, where it is effective in increasing multiple SCFA levels, including propionate, butyrate, and isobutyrate [193], brain 5-HT [44, 135], and dopamine levels [44]. However, the transplantation of microbiota for therapeutic potential in humans with neurological or psychiatric diseases remains in its infancy, with those investigations that have been undertaken being typically small scale and varying in methodology (reviewed by Settanni et al. [194]). As highlighted in relation to mouse experimentation (Box 2), performing FMT effectively is challenging and the need to perform stringent donor screening and invasive instillation mean that other options, such as altering host responses to microbiome-derived factors, and blocking or enhancing microbiome-mediated mechanisms, may ultimately gain more clinical traction and provide a basis for scalable interventions.

**KNOWLEDGE GAPS AND EMERGING CHALLENGES**

Despite the growing number of studies being reported, gut microbiome–brain research remains in its relative infancy. Five years ago, we highlighted the importance of large human cohort studies, particularly longitudinal life-course investigations, as a means to integrate the insight gained from animal and small clinical studies into a wider framework of risk exposures. Central to

this was the ‘three-hit’ model, in which genetic predisposition, the prenatal environment, and later life experiences, all contribute to an individual’s vulnerability to mental health issues. Appreciation of these issues has increased considerably and there are an increasing number of large cohort studies that aim to capture the heterogeneity of both clinical phenotypes and risk exposures that are intrinsic to real-world populations (in contrast to narrowly defined cohorts which are typically the focus of clinical trials). Such studies will allow us to continue to expand and refine emerging models of microbiome–host interaction and mental health, and increasingly exploit our newfound understanding for clinical gain.

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## AUTHOR CONTRIBUTIONS

GBR conceptualised the idea for the manuscript. APS, JMC, AMM, DJK and GBR reviewed the literature and edited the manuscript. APS, JMC and GBR drafted the manuscript. APS, JMC, AMM, DJK, M-LW, JL and GBR revised, edited and approved the final version of the manuscript.

## COMPETING INTERESTS

The authors declare no competing interests.

## ADDITIONAL INFORMATION

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